PATENT COOPERATION TREATY

PCT

REC'D 14 SEP 2005
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference M/46076-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/12423	International filing date *(day/month/year)* 06.11.2003	Priority date *(day/month/year)* 25.04.2003
International Patent Classification (IPC) or both national classification and IPC C07F9/40, C07F9/6561		
Applicant GILEAD SCIENCES, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 14 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24.11.2004	13.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Richter, H Telephone No. +49 89 2399-8539

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/12423

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-806 as originally filed

Claims, Numbers

1-250 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 196-213, 215,216,219,220,223,224,227,231,232,235,236

   because:

   ☒ the said international application, or the said claims Nos. 196-213,215,216,219,220,223,224,227,231,232,235,236 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 196-213,215,216,219,220,223,224,227,231,232,235,236 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☒ the claims, or said claims Nos. 215,216,219,220,223,224,227,231,232,235,236 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 196-213

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☒ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 103-134 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	103-134
	No:	Claims	
Inventive step (IS)	Yes:	Claims	103-134
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	103-134
	No:	Claims	

2. Citations and explanations

see separate sheet

Citations:

D11: WO 02/08241 A (GILEAD SCIENCES INC ; BECKER MARK W (US); HE GONG XIN (US); LEE WILLIA) 31 January 2002 (2002-01-31)

D16: US 2004/121316 A1 (CHEN XIAOWU ET AL) 24 June 2004 (2004-06-24)

D17: SAUBER K ET AL: "A new esterase for the cleavage of pivalic acid-containing prodrug esters of cephalosporins." ENZYME AND MICROBIAL TECHNOLOGY. JUL 1996, vol. 19, no. 1, July 1996 (1996-07), pages 15-19, XP002296487 ISSN: 0141-0229

D18: MENDES EDUARDA ET AL: "Synthesis, stability and in vitro dermal evaluation of aminocarbonyloxymethyl esters as prodrugs of carboxylic acid agents." BIOORGANIC & MEDICINAL CHEMISTRY. MAR 2002, vol. 10, no. 3, March 2002 (2002-03), pages 809-816, XP002296488 ISSN: 0968-0896

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. There was no search of claims 196-213.

2. From these claims only nos. 197, 198, 201, 202, 205, 206, 209, 211 and 212 belong to invention 13

   Although the description sufficiently discloses and supports the method of screening specified in claims 103-134 the claims directed to candidates (97, 198, 201, 202, 205, 206, 209, 211 and 212) belong to the type of so-called "reach through" claims and are not acceptable for the following reasons:

   "reach-through claims" can be defined as claims to candidate compounds and/or

uses thereof, that may be identified in the future by a screening method. They constitute an attempt to extend the invention of a screening method (see claims 103-134) to further as yet undisclosed inventions (see claims 197, 198, 201, 202, 205, 206, 209, 211 and 212). There are generally accepted principles for dealing with these claims, which are not allowable primarily by reason of lack of clarity, support and sufficient disclosure (see the trilateral study Project B3b .*"Report on Comparative Study on biotechnology patent practices")*.

Whereas claims *103-134* properly define the given invention (the screening method), the claims directed to candidates are various types of so-called reach through claims and are not allowable. Hence, claims 97, 198, 201, 202, 205, 206, 209, 211 and 212 were not susceptible of a meaningful search and consequently, the claims have not been the subject to a search by the EPO (Rule 45 EPC, Art.17(2) PCT).

2.1. The application does not meet the requirements of Article 6 PCT, because these claims 197, 198, 201, 202, 205, 206, 209, 211 and 212 are not clear.

Functional definitions as in claims 97, 198, 201, 202, 205, 206, 209, 211 and 212 are sometimes allowable in the claims. However, according to EPO-Guidelines CIII 4.7 and PCT Guidelines part II, 5.31-5.40, a functional definition can only be considered clear according to Art. 6, PCT where:

(1) the invention cannot otherwise be defined without unduly limiting the scope of the claim and

(2) the functional definition can be reduced to practice by the skilled person without undue burden, if necessary with reasonable experiments.

In the case of the present reach through claims 97, 198, 201, 202, 205, 206, 209, 211 and 212, the functional feature used to define the solution to the technical problem, is the partly the problem itself. This formulation covers all future solutions to the problem, which means:

(a) The scope of the claimed invention would **not** be unduly limited by including technical features of the claimed compounds, since it is clearly not an undue limitation of the claim to eliminate what has not yet been

invented

(b) A skilled person **cannot** reduce to practice a definition of the claimed subject matter because the compounds employed in the use claims (claims 103 to 134, 97, 198, 201, 202, 205, 206, 209, 211 and 212) have potentially limitless structural possibilities, and so there is absolutely no limit to the structural variation in the compounds which might act as a prodrug, including compounds which have yet to be made.

Consequently the requirements of the aforemetioned chapter of the guidelines whereby a functional definition might be allowed are clearly not fulfilled and so claims 97, 198, 201, 202, 205, 206, 209, 211 and 212 are not clear.

Furthermore, the examination can never with any certainty, ascertain whether or not such claims are ever distinguished over the state of the art, since this would entail testing all known organic compounds with respect of the activity of GS-7340 Ester Hydrolase on the compound or in other words testing of the compounds with respect to their activity as prodrugs. Consequently this failure to identify the scope of the claims is a further reason for a lack of clarity (Art. 6). Furthermore, since the public cannot ascertain whether or not a particular activity or product falls within the scope of such a claim, it is unclear according to Art.6 (see the comments of the Chairman of the European Technical Board of Appeal 3.3.4 .OJ 2003, Special Edition, No. 2, pages 140-165, in particular page 164).

2. 2 Lack of support and disclosure (Arts. 6/5)

According to Art. 5, C-II, 4.1, 4.2 and 4.9, the claim must contain sufficient technical disclosure of the solution to the problem. It would be an undue burden to isolate and characterize all potential drugs, without any effective pointer to their identity (C-II, 4.9) or to test every known compound and every conceivable future compound for this activity to see if it falls within the scope of the claim. Effectively, the applicant is attempting to patent what has not yet been invented and the fact that the applicant can test for the effect used to define the compounds does not necessarily confer sufficiency on the claim.

In fact there is lack of support because the application does not enable the skilled person to carry out the invention over the whole of the claimed area (Art. 5 and C-III, 6.3). Rule 5.1a) (i)-vi) requires the definition of the invention in the claim in technical terms. - This formulation is simply a definition of the problem, containing no technical pointers to the solution.

2.3. Novelty of reach-through claims

The reach-through claims (claims 197, 198, 201, 202, 205, 206, 209, 211 and 212) may well cover compounds and their uses according to claims 215, 216, 219, 220, 223, 224, 227, 231, 232, 235, 236) which are known in the state of the art. It may happen that, in the description, the applicant carries out his claimed screening method of claims 103-134 on known compounds. If some of the known compounds are found to be metabolized by *GS-7340 Ester Hydrolase*, then these compounds would satisfy the only substantial technical condition specified for the compounds of claims 197, 198, 201, 202, 205, 206, 209, 211 and 212 (the other features of these claims are of little significance because they are all common structural features of prodrugs). This would clearly demonstrate the lack of novelty of these claims. This is precisely what happened in the decision W21/01 (see Reasons for the Decision 8).

3. For the above reasons the examination of novelty and inventive step can only be carried out for claims 103-134.

Re Item IV
Lack of unity of invention

The present application lacks unity a-priori and a-posteriori for the following reasons:
Reasons for a priori non-unity:

1. Independent claim 1 relates to a method comprising the attachment of a phosphonate containing group to a non-nucleotide and determining the anti-HIV activity of the product.

In contrast thereto independent claim 2 relates to a method in which the starting compound already reveals a carboxy or phosphonate containing group. The method aims

at the determination of intercellular persistence of the compound or of a esterolytic metabolite thereof.

Independent claims 71, 73, 103, 135, 166 relate to the identification of prodrugs. Owing to their broad scope these methods are neither connected to the problem of claims 1 and 62 which is the determination of anti-HIV active compounds nor to the problem of claim 2 which is the determination of intercellular persistence.

2. The fact that there are many independent claims in the same category not only violates a requirement of Art. 6 PCT, it also indicates that there are groups of inventions which are not so linked as to form a single inventive concept. This is confirmed for instance by the different scope of the features in the method claims (e. g. claim 1 "non-nucleotide prototype" vs. the broader term in claim 62 "prototype" and claim 1 "phosphonate containing group" vs. the term "esterified phosphonate or esterified carboxyl group"). The carboxyl group part of claim 62, therefore, is not connected to claim 1 and is an additional invention.

Reasons for a posteriori non-unity:

1. The only feature which is common in claims 1, 2, and 38 is the non-nucleotide compound containing a phosphonate group. Such compound is already known in the prior art; see document D1: Hammond et al. "Alkylglyceryl Prodrugs of Phosphonoformate....", page 1622 where foscarnet and ist derivatives are described. Thus the feature "non-nucleotide compound" cannot serve as the special feature in the sense of Rule 13 PCT, linking the different subjects together.

As there is no other technical feature, that could fulfil the role of special technical feature in the sense of Rule 13 PCT, the present application lacks unity of invention.

2. Moreover, the method according to claims 1,7,14-17,19,20,27,38,42,43,62 is already known from D1, page 1622, left hand column, in which method a non-nucleotide compound (alkylglycerol) has been identified (step a). Ist phosphonate group containing derivatives have been prepared (step b) and thereafter been tested against HIV (step c); see page 1622, right hand column (Materials and Methods).
Furthermore, D2: Hakimelahi et al. (J. Med. Chem. 1995) describe the substitution of the

nucleoside analog AZT (4) with a phosphonate group to produce compound (20), with a phosphonate ester group to produce (47), (53) and (55) and of Stavudine (d4T, shown in D6, fig. 1) with a phosphonate group to produce compound (36) and the screening of these compounds for their anti-viral activity against HIV.
Hence, D2 takes away the novelty of claims 1,7,8,10,12-15,20,27,38,39,41,43,62,67.

The idea of D2 has also been applied to other nucleosides; see D3 (Kofoed), D4 (Kraus), D5 (Charvet) and D7 (WO-A-01/39724), pages 3-10. As claim 1 is not novel it can no longer serve as a general new method linking the different inventions together.

Invention 1

Methods for identifying a compound and determining the anti-HIV activity of ist phosphonate derivative. Means for the method

Claims 8,13-17,20,27,69
partly 1,7,10,12, 38-44, 62-68,70

Invention 2

Methods for identifying a compound and determining the anti-HIV activity and tissue selectivity of ist phosphonate derivative or metabolite. Means for the method.

Claim 3
partly: 1,19, 38-44

Invention 3
Methods for identifying a compound and determining the anti-HIV activity or intercellular residence time of ist phosphonate derivative or metabolite. Means for the method.

Claim 4
partly: 1,19, 38-44

Invention 4
Methods comprising selecting a non-nucleotide compound containing at least one

esterified carboxyl group and determining the intercellular persistence of the compound or a esterolytic metabolite of the esterified carboxyl thereof

Claims 6, 36
Partly 2,5,7,10,11,12,25,26, 31-34

Invention 5
Methods comprising selecting a non-nucleotide compound containing at least one esterified phosphonate group and determining the intracellular persistence of the compound or a esterolytic metabolite of the esterified phosphonate thereof

35,37
Partly 2,5,7,9 -12,25,26,31-34

Invention 6

Methods for identifying a compound and determining the anti-HIV activity and the resistance of HIV to the phosphonate derivative of the compound or metabolite thereof. Means for the method.

Claim 18
partly: 1,38-44

Invention 7

Methods for identifying a compound and determining the anti-HIV activity and susceptibility to hydrolysis of carboxyl esters by GS-7340 Ester Hydrolase. Means for the method.

Claims 46-61
partly, 1,38-44,23,24

Invention 8

Method for identifying an anti-HIV compound and substituting it with an esterified carboxylate and assaying the product for ist anti-HIV activity.

Partly 38-44, 62-68,70

Invention 9

Prodrugs and method for identifying prodrugs involving the provision of a compound having an esterified phosphonate group and contacting the compound with an extract capable of catalysing the hydrolysis of a carboxylic ester.

208,242,246
Partly: 71-72, 210, 214, 218, 222, 234, 238-241, 243,244, 247-250

Invention 10

Prodrugs and method for identifying prodrugs involving the provision of a compound having an esterified carboxylate group and contacting the compound with an extract capable of catalysing the hydrolysis of a carboxylic ester.

245, 196
Partly: 71-72, 210, 214, 218, 222, 234, 238-241,243, 244,-247-250

Invention 11

Prodrugs and method for identifying prodrugs involving the provision of a compound having an esterified phosphonate group and contacting the compound with an extract of peripheral blood having carboxylic ester hydrolase activity to produce a metabolite compound.

Partly 73-75,77-102,

Invention 12

Prodrugs and method for identifying prodrugs involving the provision of a compound having an esterified caboxylate group and contacting the compound with an extract of peripheral blood having carboxylic ester hydrolase activity to produce a metabolite compound.

76, 200,204
Partly 73-75,77-102,

Invention 13

Prodrugs and method for identifying prodrugs having an esterified phosphonate group involving the provision of a compound having an esterified phosphonate group and contacting the compound with GS-7340 Ester Hydrolase

103-134, 197,198, 201, 202,205, 206, 209, 211, 212, 215, 216, 219, 220, 223, 224,227,231,232, 235, 236

Invention 14

Prodrugs and method for identifying prodrugs having an esterified carboxyl group involving the provision of a compound having an esterified carboxyl group and contacting the compound with GS-7340 Ester Hydrolase.

135-165, 199, 203, 207, 213, 217, 221, 225, 237

Invention 15
Method for identifying prodrugs having an esterified phosphonate group involving the provision of a compound having an esterified phosphonate group and contacting the compound with an extract of peripheral blood mononuclear cells.

partly: 166-168, 170-195

Invention 16

Method for identifying prodrugs having an esterified carboxyl group involving the provision of a compound having an esterified carboxyl group and contacting the compound with an extract of peripheral blood mononuclear cells.

169
partly: 166-168, 170-195

Invention 17

Methods for identifying a compound and determining the anti-HIV activity and susceptibility to hydrolysis of ist phosphonate esters by GS-7340 Ester Hydrolase. Means for the method.

Claims partly: 1,23,24,38-44,23,24

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Invention 13:

In contrast to the compound GS-7340 which is described in D11, invention 13 is concerned with GS-7340 Ester Hydrolase. This enzyme was not mentioned earlier than in the present application. D16 (see page 475) is published later and has 4 priorities in common with the present application.

If the applicants wish to incorporate the documents mentioned inter alia at pages 805 and 806 the disclosure thereof should be included expressis verbis in the description under the conditions set out in the Guidelines C-II, 4.18 or the partial phrase "incorporated by reference" should be deleted. Thereby, where present, application serial numbers should be replaced by publication numbers.